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Molecular targets and mechanism of Longji Xiaozhong ointment in treating acute ankle sprain: A network pharmacology based analysis

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Supplementary Data

Suppl. Table S1 — Key genes (7) screened according to Degree in Cytoscape software

Gene	Betweenness	BottleNeck	Closeness	ClusteringCoefficient	Degree	DMNC	MCC	MNC	Radiality
SLC6A4	53.33333	3	10.2	0.33333	7	0.25611	14	7	5.88235
ADRB2	49.83333	5	9.81667	0.5	5	0.32413	10	5	6.17647
ADRA1B	46.5	2	9.81667	0.5	5	0.32413	10	5	6.17647
CHRM1	44.5	4	9.48333	0.4	5	0.46346	8	3	6.05882
F2	132	18	9.33333	0.5	4	0.46346	7	3	6.23529
OPRM1	1.66667	1	7.60238	0.66667	3	0.30898	4	3	5.17647
OPRD1	6.16667	1	8.03333	0.66667	3	0.30898	4	3	5.58824

Suppl. Table S2 — GO analysis of target genes in Longji Xiaozhong ointment in Nuxebra chinensis in ETCM database

GO ID	GO term description	Target Count	Target Total	P value	Odds ratio	FDR
GO:0071395	cellular response to jasmonic acid stimulus	2	85	1.42E-02	103.6	2.98E-02
GO:0008152	metabolic process	8	85	1.01E-02	3.3	2.18E-02
GO:0060748	tertiary branching involved in mammary gland duct morphogenesis	2	85	9.52E-03	138.13	2.10E-02
GO:1903416	response to glycoside	3	85	1.34E-04	124.32	6.42E-04
GO:0036376	sodium ion export across plasma membrane	3	85	6.18E-04	69.07	2.46E-03
GO:0030007	cellular potassium ion homeostasis	3	85	7.92E-04	62.16	2.85E-03
GO:0006883	cellular sodium ion homeostasis	3	85	1.44E-03	47.82	4.47E-03
GO:0086064	cell communication by electrical coupling involved in cardiac conduction	3	85	1.44E-03	47.82	4.47E-03
GO:0010248	establishment or maintenance of transmembrane electrochemical gradient	3	85	1.44E-03	47.82	4.47E-03
GO:0010107	potassium ion import	3	85	5.33E-03	25.9	1.30E-02
GO:0060119	inner ear receptor cell development	3	85	6.18E-04	69.07	2.46E-03
GO:0060384	innervation	3	85	4.04E-03	29.6	1.08E-02
GO:0090102	cochlea development	3	85	7.84E-03	21.43	1.88E-02
GO:0043524	negative regulation of neuron apoptotic process	4	85	2.53E-02	6.23	4.84E-02
GO:0043523	regulation of neuron apoptotic process	5	85	3.98E-06	43.17	2.86E-05
GO:0007214	gamma-aminobutyric acid signaling pathway	12	85	8.66E-08	99.46	1.57E-06
GO:0006821	chloride transport	16	85	9.57E-08	41.44	1.57E-06
GO:1902476	chloride transmembrane transport	16	85	1.47E-07	39	1.81E-06
GO:0071420	cellular response to histamine	5	85	1.67E-08	129.5	6.39E-07
GO:1901215	negative regulation of neuron death	3	85	2.65E-02	11.51	4.92E-02

Suppl. Table S3 — Target gene signaling pathways in Longji Xiaozhong ointment in Nuxychia chinensis in ETCM database

Pathway ID	Pathway description	Target Count	Target Total	P value	Odds ratio	FDR
R-HSA-4090294	SUMOylation of intracellular receptors	10	72	2.97E-08	49.32	1.10E-06
R-HSA-1368082	RORA activates gene expression	6	72	6.63E-08	49.32	1.23E-06
R-HSA-112314	Neurotransmitter receptors and postsynaptic signal transmission	12	72	3.49E-07	73.99	4.31E-06
R-HSA-977441	GABA A receptor activation	12	72	8.61E-07	136.59	6.60E-06
R-HSA-383280	Nuclear Receptor transcription pathway	13	72	8.91E-07	37.72	6.60E-06
R-HSA-193807	Synthesis of bile acids and bile salts via 27-hydroxycholesterol	5	72	1.72E-06	49.32	9.08E-06
R-HSA-442729	CREB phosphorylation through the activation of CaMKII	5	72	1.72E-06	49.32	9.08E-06
R-HSA-400253	Circadian Clock	7	72	1.96E-06	17.86	9.08E-06
R-HSA-438066	Unblocking of NMDA receptor, glutamate binding and activation	5	72	3.10E-06	43.52	1.15E-05
R-HSA-442982	Ras activation upon Ca2+ influx through NMDA receptor	5	72	3.10E-06	43.52	1.15E-05
R-HSA-400206	Regulation of lipid metabolism by PPARalpha	5	72	6.51E-06	36.99	2.19E-05
R-HSA-2426168	Activation of gene expression by SREBF (SREBP)	6	72	7.09E-06	21.14	2.19E-05
R-HSA-8849932	Synaptic adhesion-like molecules	5	72	8.10E-06	35.23	2.30E-05
R-HSA-193368	Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol	5	72	1.46E-05	30.83	3.85E-05
R-HSA-1368108	BMAL1:CLOCK,NPAS2 activates circadian gene expression	5	72	2.42E-05	27.4	5.98E-05
R-HSA-1989781	PPARA activates gene expression	7	72	1.18E-04	8.85	2.65E-04
R-HSA-159418	Recycling of bile acids and salts	4	72	1.22E-04	36.99	2.65E-04
R-HSA-381340	Transcriptional regulation of white adipocyte differentiation	6	72	2.21E-04	10.57	4.55E-04
R-HSA-2151201	Transcriptional activation of mitochondrial biogenesis	5	72	4.46E-04	13.45	8.68E-04
R-HSA-6794361	Neurexins and neuroligins	5	72	5.12E-04	12.98	9.48E-04

[PPAR alpha, Peroxisome proliferator-activated receptor alpha]

Suppl. Table S4 — GO analysis of target genes of Chuanxiong in Longji Xiaozhong ointment in ETCM database

GO ID	GO term description	Target Count	Target Total	P value	Odds ratio	FDR
GO:0086012	membrane depolarization during cardiac muscle cell action potential	10	713	4.91E-08	20.58	8.68E-06
GO:0000050	urea cycle	8	713	4.91E-08	16.47	8.68E-06
GO:0099133	ATP hydrolysis coupled anion transmembrane transport	8	713	4.91E-08	16.47	8.68E-06
GO:0015813	L-glutamate transport	10	713	6.62E-08	14.53	8.68E-06
GO:0035235	ionotropic glutamate receptor signaling pathway	20	713	8.50E-08	21.48	8.68E-06
GO:0010887	negative regulation of cholesterol storage	6	713	1.07E-07	24.7	8.68E-06
GO:0019228	neuronal action potential	15	713	1.09E-07	12.35	8.68E-06
GO:0006730	one-carbon metabolic process	19	713	1.09E-07	15.64	8.68E-06
GO:0010745	negative regulation of macrophage derived foam cell differentiation	8	713	1.14E-07	15.2	8.68E-06
GO:0046655	folic acid metabolic process	11	713	1.21E-07	15.1	8.68E-06
GO:0017144	drug metabolic process	12	713	1.35E-07	12.35	8.68E-06
GO:0045429	positive regulation of nitric oxide biosynthetic process	12	713	1.43E-07	7.8	8.68E-06
GO:0042572	retinol metabolic process	16	713	1.58E-07	12.75	8.87E-06
GO:0007214	gamma-aminobutyric acid signaling pathway	15	713	2.08E-07	14.82	1.03E-05
GO:0043039	tRNA aminoacylation	8	713	2.38E-07	14.12	1.03E-05
GO:0061337	cardiac conduction	15	713	2.47E-07	7.72	1.03E-05
GO:0051384	response to glucocorticoid	16	713	2.47E-07	5.99	1.03E-05
GO:0009058	biosynthetic process	18	713	2.60E-07	11.12	1.03E-05
GO:0070588	calcium ion transmembrane transport	29	713	3.03E-07	5.43	1.03E-05
GO:0060079	excitatory postsynaptic potential	28	713	3.11E-07	8.98	1.03E-05

Suppl. Table S5 — Target gene signaling pathway analysis of Chuanxiong in Longji Xiaozhong ointment in the ETCM database

Pathway ID	Pathway description	Target Count	Target Total	P value	Odds ratio	FDR
R-HSA-977441	GABA A receptor activation	12	673	9.50E-08	14.61	5.39E-06
R-HSA-211981	Xenobiotics	11	673	1.74E-07	7.92	5.39E-06
R-HSA-5365859	RA biosynthesis pathway	11	673	1.74E-07	7.92	5.39E-06
R-HSA-5576893	Phase 2 - plateau phase	12	673	1.87E-07	7.04	5.39E-06
R-HSA-5576892	Phase 0 - rapid depolarisation	27	673	1.95E-07	9.71	5.39E-06
R-HSA-383280	Nuclear Receptor transcription pathway	26	673	2.41E-07	8.07	5.55E-06
R-HSA-611105	Respiratory electron transport	26	673	3.24E-07	4.68	6.39E-06
R-HSA-112314	Neurotransmitter receptors and postsynaptic signal transmission	16	673	5.04E-07	10.55	6.95E-06
R-HSA-379716	Cytosolic tRNA aminoacylation	12	673	5.04E-07	7.92	6.95E-06
R-HSA-70614	Amino acid synthesis and interconversion (transamination)	14	673	5.04E-07	9.23	6.95E-06
R-HSA-4090294	SUMOylation of intracellular receptors	14	673	7.04E-07	7.39	8.51E-06
R-HSA-9027307	Biosynthesis of maresin-like SPMs	6	673	9.85E-07	15.83	8.51E-06
R-HSA-1475029	Reversible hydration of carbon dioxide	11	673	1.02E-06	14.51	8.51E-06
R-HSA-73817	Purine ribonucleoside monophosphate biosynthesis	10	673	1.02E-06	13.19	8.51E-06
R-HSA-112308	Presynaptic depolarization and calcium channel opening	8	673	1.02E-06	10.55	8.51E-06
R-HSA-159418	Recycling of bile acids and salts	9	673	1.04E-06	8.9	8.51E-06
R-HSA-445095	Interaction between L1 and Ankyrins	15	673	1.05E-06	7.66	8.51E-06
R-HSA-438066	Unblocking of NMDA receptor, glutamate binding and activation	9	673	1.97E-06	8.38	1.43E-05
R-HSA-196757	Metabolism of folate and pterines	9	673	1.97E-06	8.38	1.43E-05
R-HSA-2453902	The canonical retinoid cycle in rods (twilight vision)	10	673	2.22E-06	7.2	1.53E-05

Suppl. Table S6 — GO analysis of target genes of safflower in Longji Xiaozhong ointment in ETCM database

GO ID	GO term description	Target Count	Target Total	P value	Odds ratio	FDR
GO:0070989	oxidative demethylation	7	536	2.03E-08	25.56	7.66E-06
GO:0071875	adrenergic receptor signaling pathway	7	536	5.94E-08	23	7.66E-06
GO:0009235	cobalamin metabolic process	10	536	6.29E-08	15.65	7.66E-06
GO:0006123	mitochondrial electron transport, cytochrome c to oxygen	12	536	9.88E-08	17.92	7.66E-06
GO:0045429	positive regulation of nitric oxide biosynthetic process	14	536	1.02E-07	12.11	7.66E-06
GO:0048384	retinoic acid receptor signaling pathway	10	536	1.20E-07	20.54	7.66E-06
GO:0019228	neuronal action potential	12	536	1.20E-07	13.14	7.66E-06
GO:0006730	one-carbon metabolic process	16	536	1.20E-07	17.52	7.66E-06
GO:0086002	cardiac muscle cell action potential involved in contraction	9	536	1.20E-07	18.48	7.66E-06
GO:0006702	androgen biosynthetic process	7	536	1.45E-07	20.91	7.66E-06
GO:0006527	arginine catabolic process	6	536	1.49E-07	28.16	7.66E-06
GO:0042572	retinol metabolic process	17	536	1.67E-07	18.02	7.66E-06
GO:0043401	steroid hormone mediated signaling pathway	29	536	1.67E-07	15.88	7.66E-06
GO:0001523	retinoid metabolic process	15	536	2.02E-07	8.08	7.77E-06
GO:1902476	chloride transmembrane transport	20	536	2.17E-07	7.73	7.77E-06
GO:0006805	xenobiotic metabolic process	24	536	2.17E-07	9.28	7.77E-06
GO:0017144	drug metabolic process	12	536	2.26E-07	16.43	7.77E-06
GO:0006091	generation of precursor metabolites and energy	13	536	2.34E-07	8.38	7.77E-06
GO:0014070	response to organic cyclic compound	19	536	3.01E-07	4.88	8.03E-06
GO:0086012	membrane depolarization during cardiac muscle cell action potential	9	536	3.10E-07	24.64	8.03E-06

Suppl. Table S7 — Target gene signaling pathway analysis of safflower in Longji Xiaozhong ointment in ETCM database

Pathway ID	Pathway description	Target Count	Target Total	P value	Odds ratio	FDR
R-HSA-193807	Synthesis of bile acids and bile salts via 27-hydroxycholesterol	9	505	5.55E-08	12.66	3.61E-06
R-HSA-196741	Cobalamin (Cbl, vitamin B12) transport and metabolism	10	505	1.16E-07	10.05	3.61E-06
R-HSA-1475029	Reversible hydration of carbon dioxide	11	505	1.42E-07	19.34	3.61E-06
R-HSA-211981	Xenobiotics	11	505	1.95E-07	10.55	3.61E-06
R-HSA-5365859	RA biosynthesis pathway	14	505	1.95E-07	13.43	3.61E-06
R-HSA-2453902	The canonical retinoid cycle in rods (twilight vision)	12	505	1.95E-07	11.51	3.61E-06
R-HSA-9027307	Biosynthesis of maresin-like SPMs	6	505	2.33E-07	21.1	3.69E-06
R-HSA-390696	Adrenoceptors	7	505	2.81E-07	16.41	3.90E-06
R-HSA-977441	GABA A receptor activation	12	505	3.28E-07	19.47	3.95E-06
R-HSA-383280	Nuclear Receptor transcription pathway	29	505	3.62E-07	12	3.95E-06
R-HSA-5576892	Phase 0 - rapid depolarisation	23	505	4.42E-07	11.03	3.95E-06
R-HSA-4090294	SUMOylation of intracellular receptors	15	505	4.56E-07	10.55	3.95E-06
R-HSA-112314	Neurotransmitter receptors and postsynaptic signal transmission	16	505	4.99E-07	14.06	3.95E-06
R-HSA-193368	Synthesis of bile acids and bile salts via 7alpha-hydroxycholesterol	10	505	4.99E-07	8.79	3.95E-06
R-HSA-445095	Interaction between L1 and Ankyrins	15	505	6.56E-07	10.21	4.85E-06
R-HSA-70635	Urea cycle	7	505	8.10E-07	14.77	5.62E-06
R-HSA-159418	Recycling of bile acids and salts	8	505	2.35E-06	10.55	1.54E-05
R-HSA-71403	Citric acid cycle (TCA cycle)	9	505	2.80E-06	8.63	1.73E-05
R-HSA-1989781	PPARA activates gene expression	19	505	7.83E-06	3.43	4.57E-05
R-HSA-5362517	Signaling by Retinoic Acid	8	505	2.30E-05	8.04	1.28E-04